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PATENT
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On 11/15/04

TOWNSEND and TOWNSEND and CREW LLP

By: Judith Cotton

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Toyohiro Sawada *et al.*

Application No.: 09/834,410

Filed: April 12, 2001

For: TIMED-RELEASE COMPRESSION-COATED SOLID COMPOSITION FOR ORAL ADMINISTRATION

Examiner: Micah Paul Young

Art Unit: 1615

Declaration of Hiromu Kondo Under 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Hiromu Kondo, declare as follows:

1. My Curriculum Vitae is attached as Exhibit 1.

2. I am submitting this declaration to demonstrate that the instant invention is novel in view of the combination of the relevant disclosures in U.S. Patent No. 5,425,950 ("Dandiker *et al.*") and European Patent No. 0 661 945 ("Nakashima *et al.*").

3. The present invention enables drugs administered orally in a tablet formulation to be readily absorbed in the lower digestive tract. Drugs are readily absorbed in the presence of water, of which there is little in the lower digestive tract. Accordingly, the present

invention provides a drug delivery tablet that collects water in the upper digestive tract, retains the water as the tablet moves into the lower digestive tract where there is little water available to assist in drug absorption, and then releases the drug in a very short period of time which is then readily absorbed as a result of the retained water.

4. In order to accomplish the collection and retention of water, as well as the fast delivery of the drug in the lower digestive tract, the present invention consists of a tablet having at least two layers. The outer layer consists of a hydrogel forming polymer and a hydrophilic base (see Exhibit 2). The hydrophilic base acts to absorb water when the tablet is in the upper digestive tract, and the hydrogel forming polymer forms a hydrogel that retains the water as the tablet enters the lower digestive tract. The inner layer comprises a drug and a filler that erodes on contact with water (see Exhibit 2).

5. As the hydrophilic base of the outer layer absorbs water, a hydrogel forms in order to retain the water, and **the water in the tablet penetrates into the inner layer eroding the erodible filler such that the inner layer substantially becomes a solution state or suspension state**. The result is that as the tablet moves from the upper to the lower digestive tract, the tablet has an outer layer that is slowly dissolving, but substantially retaining water, and **the inner layer is substantially liquid** (see Exhibit 3). The advantage of having a substantially liquid inner layer is that when the outer layer is finally peeled away, the inner layer does not then have to dissolve in order to enable absorption of the drug. When the part of the outer layer dissolves, the inner layer is already substantially dissolved and enables rapid absorption of the drug.

6. A comparison of the percent erosion and the area under the plasma concentration curve (AUC) data from Example 9 (inventive) and Comparative Example 1 of the present invention (Table 1), as well as Example 5 (inventive) and Comparative Example 2 of the present invention (Table 2) indicate that a higher degree of erosion of the inner layer prior to partial or complete dissolution of the outer layer results in better absorption of the drug.

Table 1: Compound A: dog 20 mg/body

	erosion (%)	AUC (ng·h/ml)
Example 9 (inventive)	70	5299
Comparative ex. 1	24	3969

Table 2: Acetaminophen: dog 50 mg/body

	erosion (%)	AUC (ng·h/ml)
Example 5 (inventive)	55.2	1054
Comparative ex. 2	24.8	387

7. Dandiker *et al.* teaches a two layer tablet where the outer layer comprises a hydrophilic polymer in combination with a filler, and an inner layer comprising a drug and a filler. The outer layer of the tablet of Dandiker *et al.* allows the core to pass through the upper digestive tract and into the lower digestive tract before the core is exposed and begins to erode. In some aspects of Dandiker *et al.*, the core can erode rapidly or gradually upon exposure in the lower digestive tract (col. 3, lines 24-28). Most significantly, Dandiker *et al.* specifically states that the **core does not erode until the outer layer has been removed** such that at least some of the inner layer is exposed (col. 5, lines 24-29). Dandiker *et al.* does not teach a hydrogel or the use of a hydrogel to retain water in the core of the tablet.

8. Nakashima *et al.* teaches a tablet that consists of a single layer comprised of a hydrogel forming polymer, a hydrophilic base and a drug. The tablet of Nakashima *et al.* operates by absorbing water via the hydrophilic base and into the core of the tablet while the tablet passes through the upper digestive tract, formation of a hydrogel, and gradual dissolution of the tablet and release of the drug as the tablet travels through the lower digestive tract.

9. The examiner asserts that one of skill in the art would have been motivated to "compression coat the tablet with a hydrogel-forming polymer and use the polymer" of Nakashima *et al.* in doing so. However, neither Nakashima *et al.* nor Dandiker *et al.* teach or suggest a tablet that forms a liquid center prior to dissolution of an outer layer.

10. In order to show that the combination of Dandiker *et al.* and Nakashima *et al.* do not result in a core that is substantially eroded prior to erosion of an outer layer, tablets

were prepared according to the examples of Dandiker *et al.* and Nakashima *et al.* (see Table 3). The dosage forms were prepared, and moistened in the test solution at 37°C for 3 hours, and then the gelated part of the tablet was peeled off and the uneroded core was removed. The core was dried in a dryer overnight at 40°C and then weighed. The percentage erosion of the core tablet was calculated from the dry weight and initial weight.

11. The tablet using the core and outer layer of Dandiker *et al.* (Formulation 1 in Table 3) showed no erosion at all (last entry) of the core prior to erosion of the outer layer. In addition, the tablets using the core Dandiker *et al.* and an outer layer comprising the formulation of Nakashima *et al.* (Formulations 2 and 3 of Table 3) exhibited less than 5% erosion (last entry).

Table 3: Formulation and percent erosion of core tablet

	Formulation 1	**Formulation 2**	**Formulation 3**
Core tablet (% w/w)	example 2, Dandiker *et al.*	example 2, Dandiker *et al.*	example 10, Dandiker *et al.*
Acetaminophen	30	30	75
Microcrystalline cellulose	90	90	34.5
Pregelatinized Starch	22.5	22.5	---
Polyvinylpyrrolidone	7.5	7.5	3
Lactose	---	---	34.5
Magnesium stearate	1.5	1.5	3
Outer layer (% w/w)	example 2, Dandiker *et al.*	example 14, Nakashima *et al.*	example 14, Nakashima *et al.*
Hydroxypropyl Methylcellulose	195	---	---
Microcrystalline cellulose	30	---	---
Sodium hydrogenphosphate	22.5	---	---
Polyethylene oxide (Polyox 303)	---	197.5	197.5
PEG6000	---	50	50
Magnesium stearate	2.5	2.5	2.5
Total amount	401.5	401.5	400
Size of tablet	9.5 × 11.4R	9.5 × 11.4R	9.5 × 11.4R
Mean % erosion of core tablet (n=3)	**0**	**3.4**	**4.3**

12. Tablets of the instant invention were formulated using the example in Test Example 3 of Comparative Example 2 of the instant invention. In contrast to the formulations of

Dandiker *et al.* and Nakashima *et al.*, formulations of the instant invention demonstrate high degrees of erosion of the core prior to erosion of the outer layer (Tables 4 and 5).

Table 4: Percentage erosion of compression-coated tablet containing Compound 1

Filler	Percentage erosion (%)
Citric acid	60.3
Tartaric acid	65.7
Malic acid	75.0
PEG6000	42.6
Sucrose	48.4
PVPK30	47.6
Ascorbic acid	32.4
Succinic acid	19.2
Fumaric acid	2.0
Aspartic acid	1.4
Lactose	24.0

Table 5: Percentage erosion of compression-coated tablets containing acetaminophen

Filler	Percentage erosion (%)
Malic acid	79.3
PEG6000	84.1
Sucrose	56.1
Succinic acid	12.8
Lactose	7.6

13. In view of the fact that the instant invention displays a core that substantially erodes prior to partial or complete dissolution of the outer layer for use in a pulsed release tablet, and that the combination of Dandiker *et al.* and Nakashima *et al.* fail to teach or

suggest such a feature, the instant invention is novel and unobvious in view of Dandiker *et al.* and Nakashima *et al.* individually or in combination.

14. The time-released compression-coated tablets as presently claimed produce unexpectedly improved properties as the advantage of having a substantially liquid inner layer is that when the outer layer is finally peeled away, the inner layer does not then have to dissolve in order to enable absorption of the drug. When the outer layer partially or completely dissolves, the inner layer is already substantially dissolved and enables rapid absorption of the drug.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: November 11, 2004

Hiromu Kondo

Hiromu Kondo

BRIEF CURRICULUM VITAE OF HIROMU KONDO

Hiromu Kondo is a Japanese citizen residing in Fujieda, Shizuoka.

He received a bachelor's degree in pharmacy at Nagoya City University in 1991 and a master's degree in pharmacy at Nagoya City University in 1993.

He has been employed at Yamanouchi Pharmaceutical Co., Ltd. since April, 1993, and engaging in research on pharmaceutical development, especially biopharmacy and Drug Delivery Systems.

He received a doctor of philosophy (Pharmacy) at Nihon University in 2003.

He is a member of the Pharmaceutical Society of Japan and the Japanese Society for the Study of Xenobiotics.

He is fully aware of the reference, Dandiker et al. (U.S. Patent No. 5,425,950), Nakashima et al. (European Patent No. 0 661 945), Taniguchi et al (European Patent No. 0 709 386), Wong et al (U.S. Patent No. 5,391,381), and Kawata et al (U.S. Patent No. 4,404,183), which were cited by Examiner and also described in the specification of the present application.